### FEVER AND NEUTROPENIA IN CHILDREN

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#### NEUTROPHIL FUNCTION

- Second line of natural defense after skin and mucosal barriers
- Increased risk of infection with micro-flora
  - Skin: coagulase( –) S., S. aureus
  - Oral: viridans streptococci, anaerobs, Candida spp, HSV
  - GI: E.coli, Klebsiella, Pseudomonas , Acinetobacter , Enterobacter , Candida spp
  - RT: S. aureus, Fungi(Aspergillus, Mucomycosis, Fusarium spp)
  - UT: enteric g (–)s,
- Additional risk: other immune defect in malignancies, breakdown of skin and mucosal barriers during chemotherapy

#### DEFINITIONS

#### • Fever: Oral $T \ge$

- 38.3°C
- 38°C for > 1 h
- 38°C in 2 occasion during 12 h

• Neutropenia:

- ANC <500 cells/microL
- ANC< 1000 and expected to be <500 during 48 h. (nadir 12-14 d after chemotherapy)

> ANC = WBC x (% neut. + % bands) ÷ 100

#### CASE PRESENTATION

• A 2 y old boy brought to emergency room with fever( 38.5 Axillary) since 1 days ago. Past history and examinations are normal. CBC: WBC= 2200, lymph.= 74%, mix= 6%, neut.= 20%( ANC= 440); ESR= 16. What do you do?

- The child is a case of metabolic disorders with intermittent neutropenia. What do you do?
- The child is a new case of ALL (induction chemotherapy 7 days ago). What do you do?

### HIGH RISK CONDITIONS IN MALIGNANCY PATIENTS

- $\circ$  ANC <500 anticipated to last >7 d
- Infant with ALL or AML
- Hepatic insufficiency (ALT >5 times NL)
- Renal insufficiency (GFR <30 mL/min)
- Chronic lung disease
- Comorbid problems:
  - Hemodynamic instability
  - CVC infection
  - New neurologic, pulmonary, oral( difficult swallowing), or GI( pain, nausea, vomiting, diarrhea) symptoms

### RISK CONDITIONS IN NON-MALIGNANCY PATIENTS

PATIENIS		4 ~ · ·
LOW	MODERATE	HIGH
Well-appearing child with transient, isolated neutropenia	Well-appearing child with chronic benign neutropenia(chronic autoimmune and idiopathic neutropenia) or cyclic neutropenia	Ill-appearing child
		Severe congenital neutropenia (kostmann syndrome) or aplastic anemia
		Previous episode of complicated or life- threatening infection

# LABORATORY EVALUATION IN ALL PATIENTS O CBC/Na/K/ BUN/Cr/AST/ALT/ Bil

- B/Cs: each lumen of CVC, PVC; 3 d if fever persists, if clinical status changed or fever recured, Anaerobic BC if abdominal pain, buccal or perianal infections
- Cultures/ gram stain /imaging of sites of suspected infection
- CRP, lactate
- U/A and U/C under 3-5 yr
- CXR if any respiratory sign
- Abdominal X-ray and sonography if abdominal signs
- LP if any CNS change
- C. difficile toxin assay if diarrhea

#### EMPIRIC AB THERAPY IN HIGH RISKS

- Monotherapy: cefepime, ceftazidime, meropnem, imipenem, piperacillin/tazobactam
- + Vancomycin if: Hypotension /Pneumonia/ CV line infection/ Skin or soft tissue infection/ Grampositive on BC/ Mucositis/ Quinolones/ cytarabine
- + Aminoglycosides if: complications ( hypotension and pneumonia)/ Suspicion of resistance/ Gramnegative bloodstream infections
- + Metronidazole if : abdominal pain or blood per rectum and no cabapneme use

#### DAPTOMYCIN

- Alternative to vancomycin
- Less well studied
- Inactivated by surfactant

## EMPIRIC AB THERAPY IN LOW/MODERATE RISKS

- Eligibility:
  - Able to access medical care 24 hours daily, seven days per week
  - Able to reach the medical facility within one hour
- Therapy:
  - Oral ciprofloxacin + coamoxiclav
  - Daily follow-up
  - Observation for 4- 24 h in hospital
- Admission if :
  - Fever recrudescence,
  - New signs of infection
  - Inability to tolerate oral antibiotics
  - Identify species not susceptible to the initial empiric regimen
  - Persistence of fever beyond of two to three days

• A 2 y old boy brought to emergency room with fever( 38.5 Axillary) since 1 days ago. Past history and examinations are normal. CBC: WBC= 2200, lymph.= 74%, mix= 6%, neut.= 20%( ANC= 440); ESR= 16. What do you do?

• A 2 y old boy a case of metabolic disorders with intermittent neutropenia brought to emergency room with fever( 38.5 Axillary) since 1 days ago. Past history and examinations are normal. CBC: WBC= 2200, lymph.= 74%, mix= 6%, neut.= 20%( ANC= 440); ESR= 16. What do you do?

• A 2 y old boy a new case of ALL (induction chemotherapy 7 days ago) brought to emergency room with fever( 38.5 Axillary) since 1 days ago. Past history and examinations are normal. CBC: WBC= 2200, lymph.= 74%, mix= 6%, neut.= 20%( ANC= 440); ESR= 16. What do you do?

#### MODIFICATIONS OF INITIAL THERAPY

- Change in vital signs
- Positive BC
- Documented infection
- Fever> 4 d
- Recurrence of fever

- A 2 y old boy a new case of ALL (induction chemotherapy 7 days ago) brought to emergency room with fever. PE are normal. ANC= 440. What do you do?
- The patient treated with meropneme. After 4 days the child is febrile and stable with no focus of infection. All cultures are negative. ANC=350. What do you do?

#### PERSISTENT FEVER/NEUTROPENIA AFTER 4-7D

- DC of vancomycine if no documented infection after 3 d
- CT of the chest and sinuses
- Serial fungal serology (eg, galactomannan) twice weekly
- Biopsy of suspicious lesions
- Empiric antifungal therapy: Liposomal ampho. B or caspofungin / ampho. B complex, or ampho. B colloidal dispersion/ ampho. B deoxycholate

• A 2 y old boy a new case of ALL brought to emergency room with fever. ANC= 440. The patient treated with meropneme and after 7 days amphotericine B. After 14 days the child is febrile and stable with no focus of infection. All cultures are negative. Chest X ray and CT were NL. Galactomannan test were negative. ANC=300. What do you do?

#### PERSISTENCE OF FEVER/ NEUTROPENIA

- Continue empiric antibiotic therapy until resolution of fever or neutropenia( 10-14 d in aplastic anemia)
- Continue empiric antifungal therapy until resolution of neutropenia

- A 2 y old boy a new case of ALL brought to emergency room with fever. PE were normal. ANC= 440.
- The patient treated with cefepime. After 4 days the child is afebrile and stable with no focus of infection. All cultures are negative. ANC=350. What do you do?

### RESOLUTION OF FEVER/ PERSISTENCE OF NEUTROPENIA

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- Appeared well
- Afebrile for> 24 h
- Negative BCs
- No local infection
- Evidence of bone marrow recovery( sustained increase in platelet and ANC or APC = ANC + AMC / AB > 72 h
- > Outpatient AB s for 5-7 d

- A 2 y old boy a new case of ALL brought to emergency room with fever. PE were normal. ANC= 440.
- The patient treated with cefepime. After 4 days the child is afebrile and stable with no focus of infection. All cultures are negative. ANC=650. What do you do?

#### **RESOLUTION OF FEVER AND NEUTROPENIA**

- Negative BC for 48 h
- Resolution of fever for> 24 h
- Resolution of neutropenia (ANC >500)
- > Discharge without AB s

#### COLONY STIMULATING FACTORS

- Prophylactic use reduces neutropenia and infection
- The benefit of interventional use unanswered and may be warranted in complicated cases

#### **ENVIRONMENTAL PRECAUTIONS**

- Hand hygiene before/after the patient's room
- Neutropenic diet ( well-cooked)
- Oral hygiene (toothbrushing twice/d; oral rinses 4 times/d; dental flossing once/d atleast)
- Daily showers or baths
- Perineal hygiene
- Prohibition of plants/dried or fresh flower